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STATEMENT OF THE FACTS

In the Restriction Requirement mailed May 23, 2002, the Office alleges that there are forty-four (44) Groups or Inventions (page 2 of the Office Action):

Groups 1-43, Claims 1-66, drawn to primers consisting of SEQ ID NOs: 3-18, nested primer pairs consisting of SEQ ID NOs: 19-50, 51 and 61 and SEQ ID NOs: 62-96, 113 and 97-112, and polynucleotides containing PKD1 mutations located in regions amplified by said primer pairs, methods of detecting a mutation in a polynucleotide region, a kit containing primers to amplify a polynucleotide region and a kit containing a probe that hybridizes to the polynucleotide region. Group 44, Claim 67, drawn to a kit comprising detecting a mutation in the PKD1 gene by the binding of an antibody.

In response, on November 21, 2002, Applicants elected, with traverse, "the species, primers SEQ ID NOs: 3 and 4, nested primer pair SEQ ID NOs: 19 and 20, and polynucleotides containing PKD1 mutations located in regions amplified by said nested primers, the methods of detecting this specific region with these specific nested primer pairs and kit containing these same primer pairs to amplify said specific region (page 3 of the response)".

In a further Restriction Requirement mailed February 4, 2003 the Examiner determined that Applicants reply filed on November 21, 2002 was not fully responsive to the Restriction Requirement mailed May 23, 2002, because Applicants failed to elect "polynucleotides containing PKD1 mutations located in regions amplified by said nested primers...specific region with these specific nested primer pairs and kit containing these same primer pairs to amplify said specific region (page 2 of the Restriction Requirement)". That is, according to the Examiner, the elected primers encompass four (4) mutations in the *PKD1* gene (or SEQ ID NO:1), and Applicants failed to elect a specific *single* mutation in the *PKD1* gene.

On March 6, 2003 Applicants filed a response the further Restriction Requirement mailed February 4, 2003, and elected primers SEQ ID NOS: 3 and 4, nested primer pair SEQ ID NOS: 19 and 20, and the 3110 mutation in the *PKD1* gene (page 1 of the response). Applicants also presented arguments to traverse the second restriction requirement.

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In particular, Applicants stated in the response that according to MPEP §803.02, and In re Weber, 198 USPQ 328 (CCPA 1978) and In re Haas, 198 USPQ 334 (CCPA 1978), a restriction requirement is improper if Applicants show that there is “common utility and substantial structural relationship, disclosed as being essential to that utility” (page 3 of the March 6, 2003 response). Applicants argued that “[n]ucleic acid sequences of Groups 1-43 all *share a common utility*, namely, they comprise primers useful for selectively amplifying a region of a PKD1 gene, but not a corresponding region of a PKD1 homolog”; and that “the nucleic acid sequences of Groups 1-43 all share a structural feature that was disclosed as being essential to the above specified utility...[e.g.,] the primers or polynucleotide sequences ... specifically hybridize to a PKD1 gene” (pages 3-4 of the response). Furthermore, Applicants argue that “reference to various nucleic acids as encoding different proteins misses the invention scientifically (page 4, 2nd paragraph of the March 6, 2003 response)”. Applicants also argued that the invention relates to a method of detecting authentic *PKD1* gene sequence in a sample, and a composition, or a kit, containing such products. The claimed primers are for the purpose of detecting authentic *PKD1* gene. Therefore, the primers identify certain regions of the authentic *PKD1* gene encoding PKD1, and not “different proteins” as alleged by the Examiner on page 3 of the Restriction Requirement mailed May 23, 2002.

In the Office Action mailed September 22, 2003 the Examiner stated that neither the reply filed on March 6, 2003, nor the Examiner Interview of September 9, 2003, was fully responsive to the prior Restriction Requirement mailed February 3, 2003. That is, Applicants’ election of primers and the one SNP are allegedly located on *different* exons, and therefore the elected invention is “inoperable” (page 2 of the Office Action mailed September 22, 2003).

However, in the response filed October 21, 2003, Applicants stated that the elected mutation and primers are *not* located in different exons as alleged by the Examiner. The reason for the confusion is that Table 1 of the specification lists primers based on their “genomic coordinates”, while mutations which were identified in patients suffering from the disease are

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based on “cDNA coordinates”, which is different from the “genomic coordinates”. Hence, the elected single mutation at nucleotide position 3336, and the primers detecting the same, are both located in exon 1. Therefore, the elected claimed invention is “operable”.

Finally, in the non-final Office Action mailed January 29, 2004, the Examiner maintained and made final the Restriction Requirement, stating that:

These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequences are presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Each primer sequence and nucleotide residue are patentably distinct because they are unrelated sequences, i.e. these sequences are unrelated because *each has a different nucleotide composition and as a result different physical and biochemical properties and differs in structure and in function and in biological activity*, while primers do not encode proteins, their ability to hybridize and subsequently prime amplification is a direct effect of their characteristic nucleic acid arrangement. The Examiner reaffirms that the groups are properly separated as their inclusive products are comprised by different nucleic acid sequences and as a result, create distinct groups with variant structural and functional capacities. [emphasis added]

ACTION REQUESTED

Applicants acknowledge that claims to any non-elected invention must be cancelled prior to allowance. However, Applicants traverse the Restriction Requirement for *further* reasons stated below and request rejoinder of all withdrawn claims.

The claimed invention.

The present invention described in Applicants’ application as filed provides a method to detect authentic *PKD1* gene sequences from the pseudogene sequences that are also present in the gene. It is noteworthy, that before Applicants’ invention, it was extremely difficult to

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analyze the authentic PKD1 gene; and determine relevant mutations leading to autosomal dominant polycystic kidney disease. Further, that without the ability to analyze the entire authentic *PKD1* gene, accurate diagnosis of the disease *cannot* be achieved. In fact, in the absence of a method to detect the authentic PKD1 gene from the pseudogene, patients requiring treatment of the disease and those undergoing genetic counseling, would suffer serious setbacks and be disadvantaged.

Examination of the Claimed Sequences is Consistent with Patent Office Guidance and the Director's Waiver.

In the Restriction Requirement mailed May 23, 2002, the Examiner substantially states the reason for the Restriction Requirement, which forms the basis for further restriction requirements by the Office:

[B]ecause nucleic acids are composed of nucleotides in a myriad arrangement of base pairs wherein this arrangement can dictate various secondary structures and innumerable different resulting properties characteristics to each individual nucleotide molecule, the inventions have different structural and functional properties. Furthermore, the compositions are utilized in hybridization assays to only a specific polynucleotide region. No Group requires the invention of another since the nucleic acids of each invention can be used in many different ways and have may different characteristics including their primary and secondary sequences and resulting properties. [page 2 of the Office Action mailed May 23, 2002]

The reason for the above Restriction Requirement has basis in MPEP §2434 (Examination of Patent Applications Claiming Large Numbers of Nucleotide Sequences), which states:

Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a

restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141. ...Nucleotide sequences encoding the same protein are not considered to be independent and distinct and will continue to be examined together. In some exceptional cases, the complex nature of the claimed material may necessitate that the reasonable number of sequences to be selected be less than 10. ...

This section of the MPEP was necessitated by the explosion of nucleotide sequence information submitted with single applications during the 1990s. In some applications submitted during that time, literally thousands of sequences could be found. The intent of the policy behind MPEP §2434 was to reduce the examination of sequences to a reasonable and manageable number. According to MPEP §2434, that number is "10".

Applicants submit that all the claimed sequences of the present invention, including elected SEQ ID NOs: 3, 4, 5 and 6 and nested primers, SEQ ID NOs:19, 20, 21 and 22, hybridize to and are capable of isolating particular regions of the authentic PKD1 gene. Thus, it is submitted that the claimed invention should not be limited to just the elected sequences and SNPs of the PKD1 gene elected. Further, that this artificial limit is well within the discretion established by the Director, and examination of all sequences is completely consistent with Patent Office policy.

The Claimed Sequences Are Neither Exceptional Nor Complex.

The MPEP permits the number of sequences examined in an application to be reduced to less than 10 only under specific circumstances. See MPEP §803.04. Particularly, "[i]n some *exceptional* cases, the *complex nature* of the claimed material, for example a protein amino acid sequence reciting three dimensional folds, may necessitate that the reasonable number of sequences to be selected be less than 10." MPEP §803.04 (emphasis added).

In the present case, the Examiner has provided no evidence or argument that the claimed material is either "exceptional" or of a "complex nature" as MPEP §803.04 requires. The

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Examiner has stated that, since each nucleotide sequence may encode a different protein having structurally distinct chemical compounds and are unrelated to one another, each nucleic acid acquires a separate status in the art and results in a search that is not coextensive in scope. Yet, all claimed primer sequences hybridize to and isolate various regions, depending on the PKD1 mutation, of the same authentic PKD1 gene.

Additionally, as defined by the courts, statutes and MPEP, the “burden of search” on the Examiner need *not* be “coextensive in scope”. MPEP §803.02 clearly contemplates the examination of structurally related (not identical) species which are not coextensive in scope. The considerable overlap of the primer sequences and PKD1 gene mutations of the claimed invention is evidence Groups 1-43 are *not* divergent. In fact, the claimed primer sequences and PKD1 mutations are “coextensive in scope” because all are drawn to detecting authentic PKD1 gene..

The Claimed Sequences Do Not Encode Different Proteins.

Applicants submit that the Examiner has erroneously concluded that the “nucleic acids of each invention can be used in many different ways and have many different characteristics including their primary and secondary sequences and resulting properties (page 2 of the Restriction Requirement mailed May 23, 2002)”.

The MPEP states that “[n]ucleotide sequences encoding the same protein are not considered to be independent and distinct and will continue to be examined together.” MPEP §2434.

Applicants submit that the claimed sequences correspond and hybridize to an authentic PKD1 gene, which gene encodes for the same PKD1 protein and *not* different proteins. Therefore, all of the “[n]ucleotide sequences [encode] the same [PKD1] protein are not

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considered to be independent and distinct and [must] be examined together” as provided under MPEP §803.04 and §2434.

There exists a statutory right to claim the subject matter Applicants regard as their invention.

Additionally, Applicants respectfully submit that they have a statutory right under 35 U.S.C. §112, second paragraph, to claim the subject matter they regard as their invention as they choose. The Examiner’s actions, by requiring Applicants to elect a first amplification primer pair, a nested primer pair, and a *single* polynucleotide region containing a specific mutation that is detected specifically by the elected primer pair and nested primer pair, is tantamount to refusing to examine that which the Applicants regard as their invention.

As discussed in previous responses, MPEP §803.02, In re Weber, 198 USPQ 328 (CCPA 1978) and In re Haas, 198 USPQ 334 (CCPA 1978), all state that a restriction requirement is improper if Applicants show that there is “common utility and substantial structural relationship, disclosed as being essential to that utility” (page 3 of the March 6, 2003 response). Applicants again submit that, the nucleic acid sequences of Groups 1-43 *all share a structural feature* that is essential to the claimed utility. Again, MPEP §803.02 clearly contemplates the examination of structurally related (not identical) species, which do not share a coextensive search. Thus, the Examiner’s position is clearly not well founded in the law, and more is required for the Examiner to justify a restriction than the observation that a genus claims multiple species and the allegation that the search is not coextensive.

There is an undue burden placed on the Applicants if there is no joinder of Groups 1-43.

Applicants submit that there an unreasonable burden would be placed on the Applicants if they were required to file and prosecute many separate applications, each containing one set of nested primers that amplify only one SNP in one exon of the PKD1 gene, in order to achieve the goal of isolating and analyzing one authentic PKD1 gene. This is especially unreasonable,

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considering the fact that the ambiguous structure of the Restriction Requirement further precludes the Applicants from presenting meaningful claims commensurate with the elected species, for example, in a divisional application. Moreover, piecemeal prosecution of Applicants' invention, possibly divided between different Examiners, can lead to irresolvable inequities in claim scope and protection. It would be impracticable to enforce patents and applications that are surely guaranteed to be at different stages for several years during prosecution.

Applicants' invention covers primers and methods of using the primers to detect the authentic PKD1 gene and mutations in the PKD1 gene that result in polycystic kidney disease. There are not eight separate PKD1 genes, and to divide Applicants' invention into eight separate applications eviscerates Applicants' invention. Applicants therefore request that the restriction requirement be withdrawn, and at the very least modified with a requirement for election of species. Applicants further request that the elected species be examined, and, upon a finding that the elected species is allowable, that the entire scope of the claims be examined. In summary, the Examiner has made and maintained an erroneous restriction requirement that cuts the heart out of Applicants' invention.

Accordingly, for all the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the Restriction Requirement as applied, and the species election as applied to the non-elected SNPs and further request rejoinder of all withdrawn claims.

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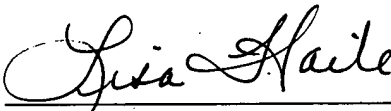
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Conclusion

No fee is believed due with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

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Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No. 28213